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(54) Title: NOVEL MULTILAYERED MATERIAL BEARING A BIOLOGICALLY ACTIVE AGENT AND THE PREPARATION THEREOF

(57) Abstract: The invention provides a material for medical use in humans and/or animals bearing a biologically active agent, said material being multilayered, as well as a device of this material and a method to produce it. The material comprises a core material, wherein said core material is formed into a body, optionally into a body having the shape of a finished device; two or more layers of coating material of which the first layer has been applied onto said core material and additional layers have been applied onto said coating material of a preceding layer; and wherein at least one of the layers comprise said biologically active agent. Characteristic for this material is that the coating material is a biopolymer, a sol-gel produced silica gel or a biologically active molecule.

Multilayered materials enable the incorporation of biologically active agents into bioactive glass. This has been possible only by adsorption, which process is difficult to control.

OBJECTS OF THE INVENTION

One object of this invention is to provide medical devices made of a material tailored to be used in the human or animal body that is multilayered wherein desired regions and/or layers, i.e. coatings, of the device are provided with one or more agents having a desired biological activity.

Another object is to achieve a medical device having coatings into which a therapeutically active agent is loaded, and from which said therapeutically active agent is released at a controlled rate.

SUMMARY OF THE INVENTION

Thus, according to one aspect, this invention concerns a material for medical use in humans and/or animals bearing a biologically active agent, said material being multilayered comprising

a) a core material, wherein said core material is formed into a body, optionally into a body having the shape of a finished device,

b) two or more layers of coating material of which the first layer has been applied onto said core material and additional layers have been applied onto said coating material of a preceding layer and

c) said biologically active agent incorporated in at least one of the coating layers.

wherein said coating material is a biopolymer, a sol-gel produced silica gel or a biologically active molecule. The method comprises the repeated steps of

i) coating said core material or a coating material of a preceding layer with a coating material which optionally can comprise a biologically active agent and

ii) optionally binding a biologically active agent to the said coating.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a schematic cross-sectional view of a rod of multilayered material.

Figure 2 shows a schematic cross-sectional view of a capsule of a multilayered material.

DETAILED DESCRIPTION OF THE INVENTION

According to invention the multilayered material bearing the biologically active agent has been shaped to a device. Said device comprises a core material formed into a body, optionally into a body having the shape of a finished device, wherein the biologically active agent is bound to the core material or to a coating material. Said core material and the coating materials of the different layers can be the same or different and said biologically active agents comprised in, or bound to said core material or said coating material can as well be the same or different.

Definitions and preferred embodiments

The term "biologically active agent" shall be understood as an agent causing a valuable effect *in vivo*, such as a bioactive effect (i.e. promoting the binding of bone

contraception and hormone replacement therapy, and for treatment of diseases such as osteoporosis, cancer, epilepsy, Parkinson´s disease and pain. The suitable biologically active agents may be, e.g. anti-inflammatory agents, anti-infective (e.g. antibiotics and antiviral agents), analgesics and analgesic combinations, antiasthmatic agents, anticonvulsants, antidepressants, antidiabetic agents, antineoplastics, anticancer agents, antipsychotics, agents used for cardiovascular diseases. The multilayered material can be tailored to release the biologically active agent or agents composed in it at a controlled rate in *in vivo* conditions.

The word "body" shall be understood to be any defined piece or continuous article such as a granule, spherulite, sheet, film, plate, stick, pin, screw, tube, fiber, hollow fiber, woven fabric or non-woven fabric, or the like also when built to resemble human or animal body parts such as ear, nose, joints, filler in plastic form, etc. or parts thereof.

The term "biopolymer" shall be understood to mean either polymers based on renewable raw materials, biodegradable or not, e.g. cellulose, or synthetic polymers which are biodegradable, e.g. polylactides.

According to a preferred embodiment, the multilayered material bears more than one biologically active agent. The different biologically active agents can be composed in the same or different coating layers or in the core material.

According to another preferred embodiment each biologically active agent can be incorporated in the core material and/or a preferred coating layer or preferred layers. Further the biologically active agent can be designed to be composed in a desired region of the core or any coating layer of the body.

According to yet another preferred embodiment of this invention, the multilayered material is formed to a device to be implanted into the human or animal body to

In the embodiment shown in figure 1 the core material 1 is bioactive glass or sol-gel produced silica gel coated with the following layers: a biodegradable polymer layer 2, a sol-gel produced silica gel or a biologically active molecule (e.g. heparin) layer 3 and another biodegradable polymer layer 4 of the same or a different polymer from the previous polymer layer 2. This arrangement, enables directed, targeted delivery of biologically active agents. The biologically active agents can be composed in both the sol-gel produced body (see example 1) or coating layer and the polymer body or coating layer (see example 2). The attachment of different layers can be improved by using different surface modification techniques, e.g. radiation induced grafting (example 2) or silylation treatment (example 3). All layers can have a different biologically active agent, if necessary. The thickness of the layers, e.g. layers 2, 3 and 4 in figure 1, can be varied widely, e.g. from about 100 nm to 1 mm depending on specific needs.

The embodiment shown schematically in figure 2 exemplifies that cumulative layers 2', 3', 4', 5' applied on the core material 1' can be tailored so as to cover only specific parts of the embodiment, in this case a capsule, but could be any device e.g. to be implanted into the human or animal body. Thus it is possible to tailor specific embodiments for specific purposes. The different layers at different locations can serve different purposes. For example capsules to be taken orally, capsules thus passing through the intestine, can be activated and/or dissolved by different pH and digestive enzymes at different locations of the intestine and activation and/or dissolution rate can be influenced by the chemical composition and area of each specific layer. Alternatively devices to be implanted can comprise asymmetrical layers with different compositions affecting different directions differently and/or layers releasing their biologically active agents at different stages of the lifecycle of the device e.g. triggered by a change in pH caused e.g. by a gradual decrease of an initial inflammation at the location of the implant.

The main field of this invention can briefly be summarized as utilization of novel multilayered materials equipped with a biologically active agent which give raise to a desired respond when brought into contact with living tissues giving said materials tailored properties for medical use in humans and animals.

The invention is disclosed in more detail by the following experiments.

EXPERIMENTAL SECTION

Example 1

Application of heparin loaded silica gel onto a grafted PLLA-co-CL copolymer

In this example, heparin is immobilized onto silica gel and then grafted PLLA (poly-L-lactide) sheets are coated with the heparinized silica-gel. Bulk heparinized silica-gel samples were obtained for the drug delivery ability tests. It is known that silica-gel can be used as a drug delivery system (Kortesuo et al. 1999).

Preparation of silica-sol

The heparin immobilized silica-sol was prepared by a two step sol-gel process using acid as a catalyst (Brinker and Scherer 1990, Ellerby et al. 1992). The following reagents were used: tetraethoxysilane (TEOS) (Aldrich), deionized water, ethanol nitric acid (HNO_3) (Merck) and ammonium hydroxide (NH_4OH). The r-value (water/TEOS molar ratio) was 3.55. Ethanol was used as a solvent to obtain better viscosity (water/ethanol molar ratio = 1). NH_4OH was used to raise pH up to 4.5. Heparin used was a sodium salt of heparin obtained from Orion Corporation (biological activity 139 I.U./mg). To obtain 100 ml hydrolysis solution, 48 g of

The extent of grafting was gravimetrically determined from the following equation:

$$E(\%) = 100 \cdot \frac{m_1 - m_0}{m_0}$$

where m_0 and m_1 are the weights of the ungrafted and the grafted sample, respectively.

The monomer solutions were purged with nitrogen for at least 30 minutes before the grafting in order to minimize the presence of oxygen during the grafting process. The grafted films were washed with ion-exchanged water for several hours in order to remove homopolymer, and dried to constant weight in vacuum at room temperature.

Tests

The following functional tests were performed: the biocompatibility of the materials was examined by using cultured cells, the release of heparin and silica were studied by dissolution testing, and the biological activity of the bound and released heparin was determined by a thrombin assay (Kang et al. 1997). From the dissolution test heparin was determined by a toluidine blue test (Smith et al. 1980 and Park et al. 1991) and silica by a spectroscopic method (Koch and Koch-Dedic 1974). Scanning electron microscopy (SEM) was used to study the morphological characteristics of the silica-gel coating. Materials were *in vitro* tested by culturing cells on materials and by measuring cytotoxicity of materials.

Dissolution test

SBF was prepared by dissolving NaCl, $NaHCO_3$, KCl, $K_2HPO_4 \times 3H_2O$, $MgCl_2 \times 6H_2O$, $CaCl_2$, Na_2SO_4, TRIZMA® HCl and TRIZMA® base as shown in Table 1.

vivo testing. Human gingival fibroblasts (Häkkinen 1995) were routinely cultured in Dulbecco's Modification of Eagle's Medium (DMEM), including 10 % (v/v) Foetal Calf Serum (FCS, kibbutz Beit Haemek, Israel), 4,500 mg/l glucose, 3.7 g/l $NaHCO_3$ and penicillin-streptomycin solution (GibcoBRL, 10,000 U/ml and 10,000 µg/ml in saline) 1 ml/l. Cells were cultured on petridishes (Ø 10 cm) at +37 °C and 5 % CO_2 atmosphere. The medium was changed every other day and the cells were harvested at confluency. Only cells from nearly confluent dishes were used for experiments.

Materials used for cell culturing were washed with 20 % ethanol and sterile deionized water. Then they were attached to culture dishes with silicone grease. Amount of cells per sample material was about 1/6 of the confluent petridish. Medium was changed every other day and cell growth was followed and investigated with a microscope.

Cytotoxicity of materials was evaluated using a modification of the lactate dehydrogenase (LDH) method (Korzeniewski and Callewaert 1983). Materials were tested as extracts. Standard 6-well plates (Nunc) were used. One confluent petridish (Ø 10 cm) was used per test. Cells were first washed with 4 ml of EDTA solution [in phosphate buffer solution (PBS), pH 7.4] and then incubated 5 minutes in 4 ml of trypsin EDTA solution (40/0.4) at +37 °C. [Trypsin stock = 2.5 % (w/v) in normal saline, GibcoBRL]. Detached cells were transferred into a 15 ml centrifuge tube and centrifuged 5 minutes at 800 rpm. Finally cells were suspended in 5 ml of medium. From this suspension 200 µl per well was added. Cells were cultured in these plates as mentioned before using 2 ml medium per well, changing medium every other day until the cultures had reached confluency.

When all cultures had almost reached confluency, the test materials were extracted. Materials (ca. 0.5 cm^2) were dipped into 20 % ethanol and rinsed with sterile deionized water. Then they were dipped into sterile eppendorf tubes and 1 ml of

A = sample slope

B = spontaneous release well slope and

C = Triton X-100 well slope.

Results

Both the dissolution rate of the silica-gel and releasing rate of heparin was examined by using the bulk gel prepared by sol-gel technique. Up to 15 %, calculated from the theoretical dry weight, of heparin was successfully immobilized to the silica-gel produced by an acid catalyzed hydrolysis reaction.

During the 24 days, 45 % of heparin loaded was released. Each heparin concentration used, 1–15 mass-% calculated from the theoretical dry weight, had similar releasing profile. Heparin concentrations were studied by toluidine blue method (Smith et al. 1980 and Park et al. 1991). Heparin released retained its biological activity as an anticoagulant when examined by the HEPRN® method.

According to information obtained from SEM studies, a uniform silica-gel coating was obtained on a surface of the acrylamide grafted PLLA-co-CL sheet. The thickness of the coating produced was 0.3 mm and its cracking after bending was minimal.

When human gingival fibroblasts were grown under cell culture conditions on coverslips, without and together with small silica-gel particles, it was found that cell growth was not influenced by the presence of the gel. Cells divided and spread normally and finally covered the silica-gel particles even though they were topographically elevated from the substratum surface. From the results of the *in vitro* test it seems obvious that silica-gels do not have any toxic or other harmful effects on fibroblasts growing in contact with the material. The present results agree with previous results indicating that silica-gels are biocompatible materials and

139 I.U./mg). To obtain 100 ml hydrolysis solution 48 g of TEOS, 45 g of deionized water and 10. 1 g of catalyst (0. 04 M HNO_3) were added to a glass beaker and stirred until the ingredients formed a homogenous solution. The silica gel coating was applied by dipping grafted polymer sheets into the homogenous hydrolysis solution.

The following functional tests were performed: the biocompatibility of the materials was examined by using cultured cells, the release of heparin and silica were studied by dissolution test and biological activity of the bound and released heparin was determined by the thrombin assay (Kang et al. 1997). From the dissolution test heparin was studied by toluidine blue test (Smith et al. 1980 and Park et al. 1991) and silica by spectroscopic method (Koch and Koch-Dedic 1974). SEM was used to study the morphological characteristics of the silica gel coating.

Results and discussion

The results from the cell culture tests, cytotoxicity test (Korzeniewski and Callewaert 1983), suggest that acrylamide grafting does not alter the biocompatibility of the PLLA-co-CL. Both contact and extract tests were carried out, and no significant differences between these results were observed.

Direct immobilization of heparin

Changing the reaction conditions, e.g. reaction time or temperature and pH of the incubation solution, could vary the amount of heparin immobilized on the grafted PLLA-co-CL. The attachment of heparin was best when acidic conditions (pH 4.5, acetic acid) were used (Table 1). Up to 98 $\mu g/cm^2$ of heparin was immobilized on the surface of the PLLA-co-CL graft polymer. The results were rather good even when only deionized water was utilized as a solvent. If the incubation solution is basic, the chemical structure of the buffering solution must be taken into account.

Silica gel immobilized heparin coating

SEM pictures of the grafted surfaces showed that a uniform, about 0.3 μm thick, silica-gel coating was obtained with the dipping technique. Cracking of the silica-gel layer was minimal after bending sheets several times 90°. Heparin released from the silica coatings during the dissolution test retained its anticoagulant activity. The releasing rate of heparin follows that observed for silica, after one week half of the immobilized heparin was released.

Example 3

The attachment of a polymeric layer on a top of bioactive glass.

In this example, the degradable bioactive glass-13 (composition: 6 % Na_2O, 12 % K_2O, 5 % MgO, 20 % CaO, 4 % P_2O_5 and 53 % Si_2O_2) (Brink 1997) is coated with biocompatible, degradable polycaprolactone polymer by using organomodified silanes as coupling agents.

Silylation of fibers

The biodegradable glass-13 fibers were prepared from glass melt (near 1100 °C) by drawing technique. After cooling down to room temperature the fibers were cut into small pieces (circa 10 cm long). These fibers were placed into a 50 ml falcon tube and the tube was filled with silylation reagent (2 % of dichlorodimethylsilane ($C_2H_6Cl_2Si$) in trichloromethane ($CHCl_3$) solution). The silylation lasted for 10 min. Before washing the fibers carefully with deionized water, the silylation coating was let to stabilize for 24 h. The washed, silylated fibers were dried in a vacuum deccicator for an additional 24 h.

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CLAIMS

1. A material for medical use in humans and/or animals bearing a biologically active agent, said material being multilayered comprising

a) a core material, wherein said core material is formed into a body, optionally into a body having the shape of a finished device,

b) two or more layers of coating material of which the first layer has been applied onto said core material and additional layers have been applied onto said coating material of a preceding layer and

c) said biologically active agent incorporated in at least one of the coating layers,

characterized in that said coating material is a biopolymer, a sol-gel produced silica gel or a biologically active molecule.

2. The material according to claim 1 **characterized** in that the core material is a biodegradable silica body, e.g. bioactive glass or sol-gel produced silica gel, or a biopolymer, e.g. a polylactide or a cellulose.

3. The material according to claim 1 or 2, **characterized** in that said coating material is a biopolymer, e.g. a polylactide or a cellulose.

4. The material according to claim 1 or 2, **characterized** in that said coating material is a sol-gel produced silica gel.

5. The material according to claim 1 or 2, **characterized** in that said coating material is heparin.

- a growth factor producing virus,
- a growth factor inhibitor,
- an integrin blocker (e.g. a IIa/IIIb inhibitor)
- an oligonucleotide or
- a complete functional or partial gene in sense or antisense orientation in a suitable expression vector or any other expression vector construct

for local delivery of said biologically active agent.

12. The material according to claim 9, **characterized** in that it is shaped to a stent, the inner wall of which is provided with a biologically active agent; which is

- an inorganic ion or a polymer thereof,
- silica gel as such or silica gel loaded with a therapeutical agent,
- heparin,
- a growth factor,
- a growth factor producing virus,
- a growth factor inhibitor,
- an integrin blocker (e.g. a IIa/IIIb inhibitor),
- an oligonucleotide or
- a complete or partial functional gene in sense or antisense orientation in a suitable expression vector or any other expression vector construct; and

which biologically active agent is released at a controlled rate in *in vivo* conditions.

13. A device made of a material, useful for finishing into a device of a material for medical use in humans and/or animals, said material bearing or being capable of binding a biologically active agent, wherein said material is multilayered and formed into a body of the shape of a finished device comprising

a) a core material, wherein said core material is formed into a body, optionally into a body having the shape of a finished device,

16. The method according to claim 14 or 15, **characterized** in that the attachment of a coating layer is improved by using surface modification techniques of the surface to be coated, i.e. the core surface or the surface of the previous coating layer.

17. The method according to claim 16, **characterized** in that the surface modification technique used is radiation induced grafting or silylation treatment.

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/11/00

International application No.
PCT/FI 00/00730

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INTERNATIONAL SEARCH REPORT

International application No.
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A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61L 27/00, A61L 27/54, A61L 31/00, A61L 31/16
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	US 5876433 A (ANTHONY C. LUNN), 2 March 1999 (02.03.99), claims 1-2 --	1-17
A	EP 0923953 A2 (SCHNEIDER (USA) INC.), 23 June 1999 (23.06.99), claims 1-9,21 --	1-17

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
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